REMARKS

Claims 2-9 are pending in this application. Applicant acknowledges the Examiner's withdrawal of her objection to the specification, her rejection of claims 1-6 for lack of enablement, and her rejection of claim 1 for anticipation.

Rejection under 35 U.S.C., § 112, first paragraph

Written Description

The Office rejected claims 2-9 as failing to comply with the written description requirement of 35 U.S.C. §112 because the amino acid and nucleotide sequences of the protein to be modified are not disclosed. Applicant respectfully disagrees with the Office's assessment.

The Office argues that there are several forms of human antithrombin III, and cites the "Aalborg" and "Budapest" antithrombin III variants as examples. *Office Action*, page 4. Both the Aalborg and Budapest variants, however, exhibit pathological deficiencies in their factor Xa inactivating abilities. *See* P.J. Sorenson et. al., "Distinction of Two Pathologic Antithrombin III Molecules: Antithrombin III 'Aalborg' and Antithrombin III 'Budapest'," *Throm. Res.* 26: 211-219, 1982. Applicant, on the other hand, defined natural human antithrombin as "a main control factor in the blood coagulation system which controls activities of main coagulating enzymes, such as thrombin, activated factor X (factor Xa), activated factor IX (factor IXa), etc." *Specification*, page 2, lines 21-25. Neither variant cited by the Office fits into the definition of natural human antithrombin as provided by the specification because each fails to function as a main control factor in the blood coagulation system. Accordingly, the specification clearly indicates to a person skilled in the art

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that the protein to be modified is the normal, functional human antithrombin III, not a non-functional variant such as antithrombin III "Aalborg" or "Budapest". Applicant respectfully requests that the §112, first paragraph rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Office reiterated its rejection of claim 5, and rejected claim 9, under 35 U.S.C. §103 as obvious in light of J.A. Huntington *et.al.*, *Biochemistry*, 1998, 37: 3272-3277, J.A. Huntington *et.al., Biochemistry*, 1996, 35: 8495-8503, and common knowledge in molecular biology. Applicant respectfully requests that the Office reconsider this rejection.

To establish a case of obviousness, the Office must show that there is a motivation to combine the references cited against the application, that there is a reasonable expectation of success, and that the prior art teaches all of the claimed limitations. MPEP § 2143. Applicant respectfully submits that the Office has failed to establish a motivation to combine the references and a reasonable expectation of success. Further, the cited references fail to disclose all of the recited claim elements.

A. No Motivation to Combine References

The Office maintains that motivation to combine the cited references comes from a statement in Huntington's 1998 paper indicating a need for a clinically-useful heparin-independent antithrombin III mutant. *Office Action*, p. 6. While Huntington may provide motivation to create a clinically-useful variant by substituting cysteine at amino acid position 380, a person skilled in the art would not find motivation to try other amino acids, nor would such a person be motivated to try the 12 specific

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amino acids recited in claims 5 and 9. Huntington provides insufficient motivation to combine elements of the prior art to produce the claimed invention.

Applicant reiterates that Huntington's language provides no motivation to substitute amino acids, other than cysteine or tryptophan at position 380 of antithrombin III. Huntington is successful with his two selections, thereby providing no motivation to select others because success has been achieved. While two successes within a genus of 20 amino acids may render it obvious to try some of the remaining 18 amino acids, "obvious to try" is not the standard for a §103 rejection. *See In re Dow Chemical Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d. 1529, 1532 (Fed. Cir. 1988). Given Huntington's success with cysteine and tryptophan, selecting others would lead to additional and perhaps unnecessary experimentation.

Furthermore, the selection of two amino acids in Huntington provides no motivation to select the 12 specific amino acids recited in claims 5 and 9. Again, in light of Huntington's success with cystein and tryptophan, no guidance is given as to the characteristics or function of other appropriate amino acids. Accordingly, Huntington provides no motivation to substitute cysteine and tryptophan with any of the 12 specific amino acids included in claims 5 and 9.

B. No Reasonable Expectation of Success

According to the Office, Huntington has shown that the probability of success is high when substituting position 380 in antithrombin III with an alternative amino acid to create a heparin-independent mutant. *Office Action*, p. 7. The Office characterized this rate of success as "about 20%." *Id.* Applicant calculates Huntington's success at 10%, with two demonstrated successes out of a possible

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20. This means that 90% of potential substitutions are functionally unknown in the art. Therefore, the likelihood of success in finding a substitution rendering the antithrombin III mutant heparin independent is not high, but rather considerably low, given that approximately 90% of potential substitutions are unknown.

The Office also relies on the fact that Applicant successfully created heparin-independent mutants with multiple amino acids as confirmation of the probability of success. *Office Action*, p 7. However, reliance on the present application for evidence of probability of success is inappropriate, because such a reliance is based on hindsight. *See* MPEP § 2141.01.

As previously argued, information within Huntington's 1996 paper, relied on by the Office, further decreases the likelihood of success of random amino acid substitution. In his paper, Huntington states that the inhibitory action of antithrombin III is "very sensitive to the correct folding of antithrombin." J. A. Huntington *et.al.*, *Biochemistry* 1996, 35: 8495-8503 at page 8498. Any mechanism that exhibits a high level of structural sensitivity is likely going to be similarly sensitive to changes to its structure. Accordingly, a person skilled in the art would know that substituting alternate amino acids into known functional sites of antithrombin III would not necessarily be successful.

Because 10% is not a particularly high success rate, because a high success rate may not be inferred from the instant specification, and because of the known structural sensitivity of antithrombin III, there is no reasonable expectation of success found within the prior art.

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C. Not All Elements Taught by Cited References

Finally, the cited references disclose antithrombin variants substituted with cysteine and tryptophan. Claims 5 and 9 recite substitution with alanine, aspartic acid, glycine, histidine, isoleucine, leucine, asparagnine, proline, arginine, threonine, tyrosine, and valine. The Office has not cited any reference that uses any of the claimed amino acids in an antithrombin variant, nor any reference providing for a DNA encoding a human antithrombin III variant substituted at position 380 with alanine, aspartic acid, glycine, histidine, isoleucine, leucine, asparagnine, proline, arginine, threonine, tyrosine, and valine, as required by claim 9. As a result, not all of the claimed limitations are taught by the prior art cited by the Office.

Because the cited references fail to provide any motivation to combine their teachings, do not provide a person skilled in the art with an expectation that substituting the claimed amino acids into position 380 of antithrombin III will be successful, and do not disclose all of the claimed limitations, Applicant respectfully requests that the rejection be withdrawn.

Applicants respectfully request that this Response under 37 C.F.R. § 1.116, be considered by the Examiner. Applicants submit that the entry of this response would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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